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(54) Title: THROMBIN OR FACTOR Xa INHIBITORS

(57) Abstract: This invention relates generally to heteroaryl-phenyl substituted compounds that are inhibitors of trypsin-like serine protease enzymes, especially factor Xa or thrombin, pharmaceutical compositions containing the same, and methods of using the same as anticoagulant agents for treatment and prevention of thromboembolic disorders.

TITLE

Thrombin or Factor Xa Inhibitors

FIELD OF THE INVENTION

This invention relates generally to heteroaryl-phenyl substituted compounds that are inhibitors of trypsin-like serine protease enzymes, especially factor Xa or thrombin, pharmaceutical compositions containing the same, and methods of using the same as anticoagulant agents for treatment and prevention of thromboembolic disorders.

BACKGROUND OF THE INVENTION

Activated factor Xa, whose major practical role is the generation of thrombin by the limited proteolysis of prothrombin, holds a central position that links the intrinsic and extrinsic activation mechanisms in the final common pathway of blood coagulation. The generation of thrombin, the final serine protease in the pathway to generate a fibrin clot, from its precursor is amplified by formation of prothrombinase complex (factor Xa, factor V, Ca^{2+} and phospholipid). Since it is calculated that one molecule of factor Xa can generate 138 molecules of thrombin, inhibition of factor Xa may be more efficient than inactivation of thrombin in interrupting the blood coagulation system.

Therefore, efficacious and specific inhibitors of factor Xa, thrombin, or both are needed as potentially valuable therapeutic agents for the treatment of thromboembolic disorders. It is thus desirable to discover new factor Xa, thrombin, or both inhibitors.

SUMMARY OF THE INVENTION

Accordingly, one object of the present invention is to provide novel heteroaryl-phenyl substituted compounds that are useful as factor Xa inhibitors or pharmaceutically acceptable salts or prodrugs thereof.

It is another object of the present invention to provide pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

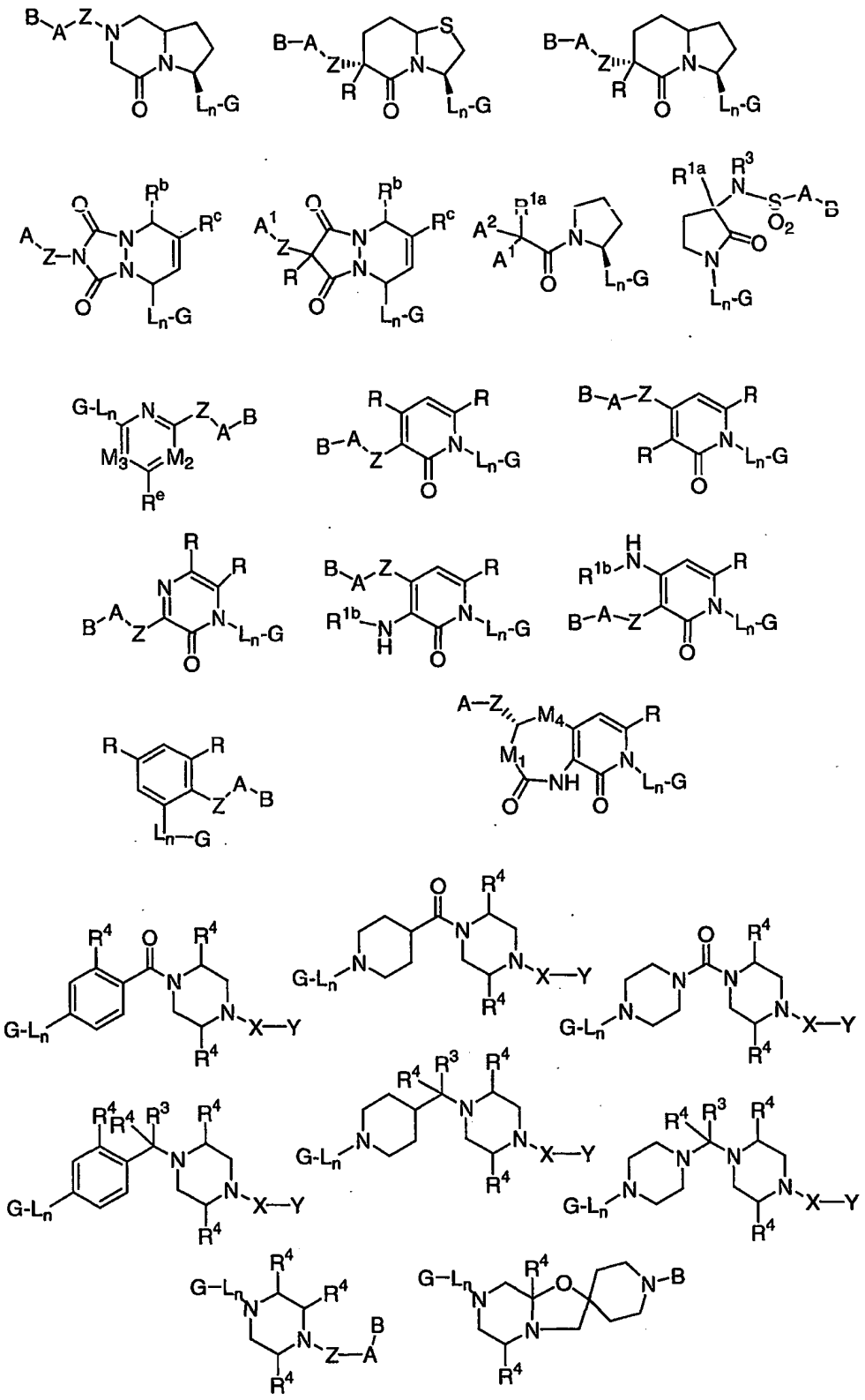
It is another object of the present invention to provide a method for treating thromboembolic disorders comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

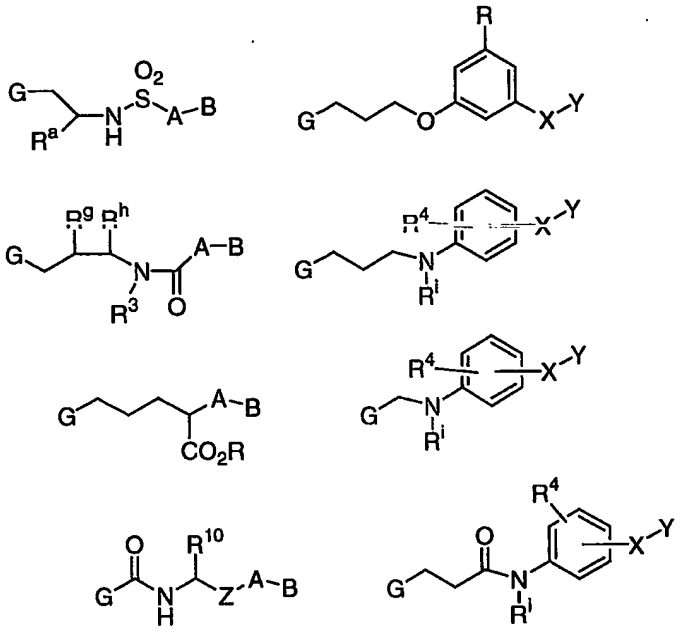
It is another object of the present invention to provide novel compounds for use in therapy.

It is another object of the present invention to provide the use of novel compounds for the manufacture of a medicament for the treatment of thrombosis or a disease mediated by factor Xa.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

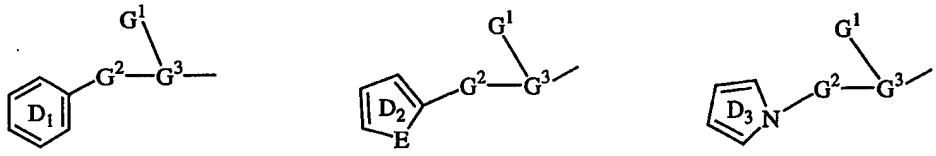
[1] Thus, in an embodiment, the present invention provides a novel compound selected from the group:





or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

G is selected from formulas Ia-Ic:



Ia Ib Ic

ring D_1 is selected from pyridine, pyrazine, pyridazine, and pyrimidine and is substituted with 1 D_{1a} and 0-1 D_{1b};

ring D_2 is a 5-membered heteroaromatic ring system comprising E, carbon atoms, and 0-3 N atoms, wherein E is selected from O, S, and N-D_{1c} and ring D_2 is substituted with 1 D_{1a} and 0-1 D_{1b};

ring D_3 is a 5-membered heteroaromatic ring system comprising carbon atoms and from 0-3 additional N atoms and ring D_3 is substituted with 1 D_{1a} and 0-1 D_{1b};

G^1 is selected from H, C_{1-4} alkyl, F, Cl, Br, I, OH, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2CH_3$, CN, $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl)$_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), $CH_2CH_2N(C_{1-3}$ alkyl)$_2$, $(CR^8R^9)_tNR^7R^8$, $(CR^8R^9)_tC(O)NR^7R^8$, and OCF_3;

D_{1a} is selected from H, C_{1-4} alkyl, F, Cl, Br, I, OH, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2CH_3$, CN, $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl)$_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), $CH_2CH_2N(C_{1-3}$ alkyl)$_2$, $(CR^8R^9)_tNR^7R^8$, $(CR^8R^9)_tC(O)NR^7R^8$, and OCF_3;

D_{1b} is selected from H, C_{1-4} alkyl, F, Cl, Br, I, OH, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2CH_3$, CN, $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl)$_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), $CH_2CH_2N(C_{1-3}$ alkyl)$_2$, $(CR^8R^9)_tNR^7R^8$, $(CR^8R^9)_tC(O)NR^7R^8$, and OCF_3;

D_{1c} is selected from H, C_{1-4} alkyl, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2CH_3$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl)$_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), $CH_2CH_2N(C_{1-3}$ alkyl)$_2$, $(CR^8R^9)_tNR^7R^8$, $(CR^8R^9)_tC(O)NR^7R^8$, and OCF_3;

G^2 is absent or is selected from CH_2, $C(O)$, O, NR^3, $S(O)_p$, CH_2CH_2, $C(O)CH_2$, $CH_2C(O)$, OCH_2, CH_2O, NR^3CH_2, CH_2NR^3, $S(O)_pCH_2$, $CH_2S(O)_p$, $CH_2CH_2CH_2$, $C(O)CH_2CH_2$, $CH_2C(O)CH_2$, $CH_2CH_2C(O)$, OCH_2CH_2, CH_2OCH_2, CH_2CH_2O, $NR^3CH_2CH_2$, $CH_2NR^3CH_2$, $CH_2CH_2NR^3$, $S(O)_pCH_2CH_2$, $CH_2S(O)_pCH_2$, and $CH_2CH_2S(O)_p$;

G^3 is phenyl, naphthyl, or a 5-10 membered heteroaryl consisting of carbon atoms and from 1-3 heteroatoms selected from N, O, and S;

L_n is a linker which is absent or is selected from O, S, $S(O)_2$, CH_2, *NHC(O), *C(O)NH, *$S(O)_2$NH, *$NHS(O)_2$, *CH_2NHC(O), *$CH(R^a)$NHC(O), *CH_2NHC(O)CH_2, and *$CH(R^a)$NHC(O)CH_2, provided that L_n and M do not form an O-N or S-N bond and the * indicates where L_n is bonded to G;

M^1 is absent or is selected from CHR, O, and NR^2;

M^2 is N or CR^f;

M^3 is N or CR^d;

provided that only one of M^2 and M^3 is N;

M^4 is selected from NR^2, CR^f, and C(O);

R^a is selected from $C(O)C(O)OR^3$, $C(O)C(O)NR^2R^{2a}$, and C(O)-A;

R^b is selected from H, R, phenyl, C_{1-10} alkyl, and C_{2-5} alkenyl;

R^c is selected from H and C_{1-6} alkyl;

alternatively, R^b and R^c together are $-(CH_2)_4-$;

R^d is selected from H, F, and Cl;

R^e is selected from H, $N(CH_3)(CH_2CO_2H)$ and S-(5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4);

alternatively, R^d and R^e combine to form $-NR^3-C(O)-C(R^{1g}R^3)-NR^3-$ or $-N=CR^2-NR^3-$;

R^f is selected from H, F, and Cl;

alternatively, R^e and R^f combine to form $-NR^3-C(R^{1g}R^3)-C(O)-NR^3-$ or $-NR^3-CR^2=N-$;

R^g is selected from H, CH_2OR^3, $CH_2C(O)OR^3$, C_{1-4} alkyl, $C(O)NH_2$, and NH_2;

R^h is selected from H, CH_2-phenyl, CH_2CH_2-phenyl, and CH=CH-phenyl;

R^i is selected from $SO_2CH_2C(O)OR^3$, $C(O)CH_2C(O)OR^3$, and $C(O)OR^3$;

R is selected from H, Cl, F, Br, I, $(CH_2)_tOR^3$, C_{1-4} alkyl, benzyl, OCF_3, CF_3, $C(O)NR^7R^8$, $(CH_2)_tNR^2SO_2$-C_{1-4} alkyl, and $(CR^8R^9)_tNR^7R^8$;

Z is selected from a $(CR^8R^9)_{1-4}$, $(CR^8R^9)_rO(CR^8R^9)_r$, $(CR^8R^9)_rNR^3(CR^8R^9)_r$, $(CR^8R^9)_rNR^3C(=CHR^8)(CR^8R^9)_r$, $(CR^8R^9)_rC(O)(CR^8R^9)_r$, $(CR^8R^9)_rC(O)O(CR^8R^9)_r$, $(CR^8R^9)_rOC(O)(CR^8R^9)_r$, $(CR^8R^9)_rC(O)NR^3(CR^8R^9)_r$, $(CR^8R^9)_rNR^3C(O)(CR^8R^9)_r$, $(CR^8R^9)_rOC(O)O(CR^8R^9)_r$, $(CH_2)_rOC(O)NR^3(CR^8R^9)_r$, $(CR^8R^9)_rNR^3C(O)O(CR^8R^9)_r$, $(CH_2)_rNR^3C(O)NR^3(CR^8R^9)_r$, $(CR^8R^9)_rS(O)_p(CR^8R^9)_r$, $(CR^8R^9)_rS(O)_2(CH=CH)$, $(CCR^8R^9)_rSO_2NR^3(CR^8R^9)_r$, $(CR^8R^9)_rNR^3SO_2(CR^8R^9)_r$, and $(CR^8R^9)_rNR^3SO_2NR^3(CR^8R^9)_r$, provided that Z does not form a N-N, N-O, N-S, NCH_2N, NCH_2O, or NCH_2S bond with the groups to which Z is attached;

R^{1a} is selected from H, $-(CH_2)_r-R^{1b}$, $-CH=CH-R^{1b}$, NCH_2R^{1c}, OCH_2R^{1c}, SCH_2R^{1c}, $NH(CH_2)_2(CH_2)_tR^{1b}$, $O(CH_2)_2(CH_2)_tR^{1b}$, $S(CH_2)_2(CH_2)_tR^{1b}$, $S(O)_p(CH_2)_rR^{1d}$, $O(CH_2)_rR^{1d}$, $NR^3(CH_2)_rR^{1d}$, $OC(O)NR^3(CH_2)_rR^{1d}$, $NR^3C(O)NR^3(CH_2)_rR^{1d}$, $NR^3C(O)O(CH_2)_rR^{1d}$, and $NR^3C(O)(CH_2)_rR^{1d}$, provided that R^{1a} forms other than an N-halo, N-N, N-S, N-O, or N-CN bond;

R^{1b} is selected from H, C_{1-3} alkyl, F, Cl, Br, I, -CN, -CHO, $(CF_2)_rCF_3$, $(CH_2)_rOR^2$, NR^2R^{2a}, $C(O)R^{2c}$, $OC(O)R^2$, $(CF_2)_rCO_2R^{2a}$, $S(O)_pR^{2b}$, $NR^2(CH_2)_rOR^2$, $C(=NR^{2c})NR^2R^{2a}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NHR^{2b}$, $NR^2C(O)_2R^{2a}$, $OC(O)NR^{2a}R^{2b}$, $C(O)NR^2R^{2a}$, $C(O)NR^2(CH_2)_rOR^2$, $SO_2NR^2R^{2a}$, $NR^2SO_2R^{2b}$, C_{3-6}

carbocycle substituted with 0-2 R^{4a}, and 5-10 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-2 R^{4a}, provided that R^{1b} forms other than an N-halo, N-N, N-S, N-O, or N-CN bond;

R^{1c} is selected from H, $CH(CH_2OR^2)_2$, $C(O)R^{2c}$, $C(O)NR^2R^{2a}$, $S(O)R^{2b}$, $S(O)_2R^{2b}$, and $SO_2NR^2R^{2a}$;

R^{1d} is selected from C_{3-13} carbocycle substituted with 0-2 R^{4a}, and 5-13 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-2 R^{4a}, provided that R^{1d} forms other than an N-N, N-S, or N-O bond;

R^{1g} is selected from H, C_{1-6} alkyl, and C_{1-6} alkyl substituted with A;

R^2, at each occurrence, is selected from H, CF_3, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2a}, at each occurrence, is selected from H, CF_3, C_{1-6} alkyl, benzyl, C_{3-6} cycloalkylmethyl substituted with 0-2 R^{4b}, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4

heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2b}, at each occurrence, is selected from CF_3, C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2c}, at each occurrence, is selected from CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

alternatively, R^2 and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

R^3, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

R^{3a}, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

R^{3b}, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

R^{3c}, at each occurrence, is selected from C_{1-4} alkyl, and phenyl;

R^{3d}, at each occurrence, is selected from H, C_{1-4} alkyl, C_{1-4} alkyl-phenyl, and $C(=O)R^{3c}$;

A is selected from:

C_{3-10} carbocyclic residue substituted with 0-2 R^4, and

5-12 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4;

A^1 is H or A;

alternatively, A and A^1 and the carbon to which they are attached combine to form fluorene;

A^2 is selected from H, A, and CHA^3A^4;

A^3 is selected from H, A, C_{1-4} alkyl, and $-(CH_2)_rNR^2R^{2a}$;

A^4 is H or A;

B is selected from: H, Y, and X-Y, provided that Z and B are attached to different atoms on A;

X is selected from $-(CR^2R^{2a})_{1-4}-$, $-CR^2(CR^2R^{2b})(CH_2)_t-$, $-C(O)-$, $-C(=NR^{1c})-$, $-CR^2(NR^{1c}R^2)-$, $-CR^2(OR^2)-$, $-CR^2(SR^2)-$, $-C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-SCR^2R^{2a}-$, $-S(O)CR^2R^{2a}-$, $-S(O)_2CR^2R^{2a}-$, $-CR^2R^{2a}S-$,

$-CR^2R^{2a}S(O)-$, $-CR^2R^{2a}S(O)_2-$, $-S(O)_2NR^2-$, $-NR^2S(O)_2-$, $-NR^2S(O)_2CR^2R^{2a}-$, $-CR^2R^{2a}S(O)_2NR^2-$, $-NR^2S(O)_2NR^2-$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-C(O)NR^2CR^2R^{2a}-$, $-NR^2C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)NR^2-$, $-CR^2R^{2a}NR^2C(O)-$, $-NR^2C(O)O-$, $-OC(O)NR^2-$, $-NR^2C(O)NR^2-$, $-NR^2-$, $-NR^2CR^2R^{2a}-$, $-CR^2R^{2a}NR^2-$, O, $-CR^2R^{2a}O-$, and $-OCR^2R^{2a}-$;

Y is selected from:

C_{3-10} carbocyclic residue substituted with 0-2 R^{4a}, and 5-12 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

alternatively, Z-A-B combine to form S-C_{1-6} alkyl;

R^4, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, $(CH_2)_rF$, $(CH_2)_rCl$, $(CH_2)_rBr$, $(CH_2)_rI$, C_{1-4} alkyl, $(CH_2)_rCN$, $(CH_2)_rNO_2$, $(CH_2)_rNR^2R^{2a}$, $C(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, $C(=NS(O)_2R^5)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $C(O)NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, $(CF_2)_rCF_3$, $(CH_2)_r$-CF_3, NCH_2R^{1c}, OCH_2R^{1c}, SCH_2R^{1c}, $N(CH_2)_2(CH_2)_tR^{1b}$, $O(CH_2)_2(CH_2)_tR^{1b}$, $S(CH_2)_2(CH_2)_tR^{1b}$, 5-6 membered carbocycle substituted with 0-1 R^5, and 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-1 R^5;

R^{4a}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, $(CF_2)_rCF_3$, $(CH_2)_r$-CF_3, $(CH_2)_r$-F, $(CH_2)_r$-Br, $(CH_2)_r$-Cl,

C_{1-4} alkyl, $(CH_2)_rCN$, $(CH_2)_rNO_2$, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $(CH_2)_rN{=}CHOR^3$, $C(O)NH(CH_2)_2NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $NR^2SO_2R^5$, $C(O)NHSO_2$-C_{1-4} alkyl, $S(O)_pR^5$, 5-6 membered carbocycle substituted with 0-1 R^5, and 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-1 R^5;

R^{4b}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^3$, $(CH_2)_r$-F, $(CH_2)_r$-Cl, $(CH_2)_r$-Br, $(CH_2)_r$-I, C_{1-4} alkyl, $(CH_2)_r$-CN, $(CH_2)_r$-NO_2, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $NR^3C(O)NR^3R^{3a}$, $C(=NR^3)NR^3R^{3a}$, $NR^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, $NR^3SO_2NR^3R^{3a}$, NR^3SO_2-C_{1-4} alkyl, $NR^3SO_2CF_3$, NR^3SO_2-phenyl, $S(O)_pCF_3$, $S(O)_p$-C_{1-4} alkyl, $S(O)_p$-phenyl, $(CH_2)_rCF_3$, and $(CF_2)_rCF_3$;

R^5, at each occurrence, is selected from H, C_{1-6} alkyl, =O, $(CH_2)_rOR^3$, F, Cl, Br, I, -CN, NO_2, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $NR^3C(O)NR^3R^{3a}$, $CH(=NOR^{3d})$, $C(=NR^3)NR^3R^{3a}$, $NR^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, $NR^3SO_2NR^3R^{3a}$, NR^3SO_2-C_{1-4} alkyl, $NR^3SO_2CF_3$, NR^3SO_2-phenyl, $S(O)_pCF_3$, $S(O)_p$-C_{1-4} alkyl, $S(O)_p$-phenyl, $(CF_2)_rCF_3$, phenyl substituted with 0-2 R^6, naphthyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6;

R^6, at each occurrence, is selected from H, OH, $(CH_2)_rOR^2$, halo, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $C(=NH)NH_2$, $NHC(=NH)NH_2$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, and $NR^2SO_2C_{1-4}$ alkyl;

R^7, at each occurrence, is selected from H, OH, C_{1-4} alkoxycarbonyl, C_{6-10} aryloxy, C_{6-10} aryloxycarbonyl, C_{6-10} arylmethylcarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{6-10} arylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{1-6} alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C_{1-4} alkoxycarbonyl;

R^8, at each occurrence, is selected from H, C_{1-6} alkyl, and $(CH_2)_n$-phenyl;

alternatively, R^7 and R^8, when attached to the same nitrogen, combine to form a 5-6 membered heterocyclic ring consisting of carbon atoms and 0-2 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^9, at each occurrence, is selected from H, C_{1-6} alkyl and $(CH_2)_n$-phenyl;

R^{10} is selected from H, phenyl substituted with 0-2 R^{4a}, and naphthyl substituted with 0-2 R^{4a};

n, at each occurrence, is selected from 0, 1, 2, and 3;

m, at each occurrence, is selected from 0, 1, and 2;

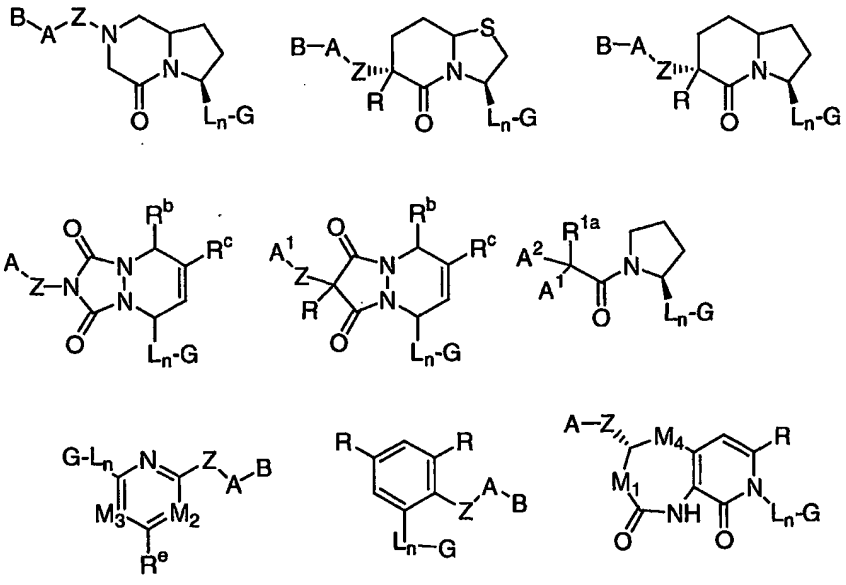
p, at each occurrence, is selected from 0, 1, and 2;

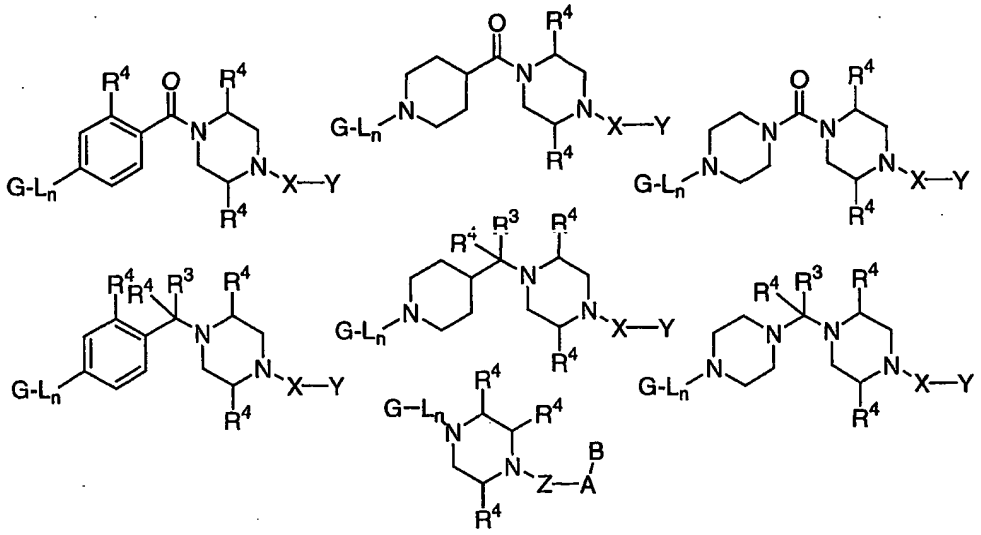
r, at each occurrence, is selected from 0, 1, 2, and 3;

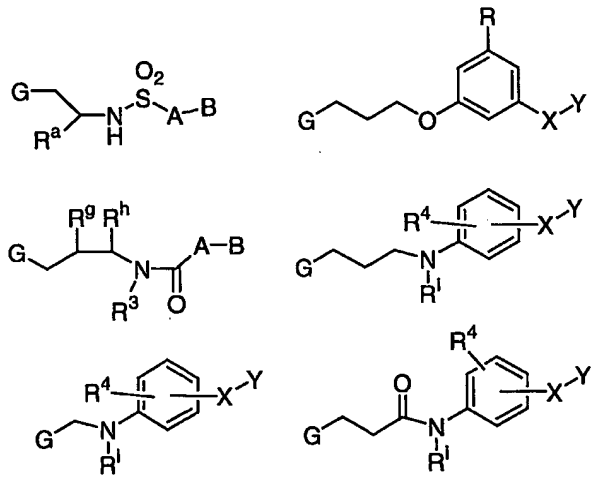
s, at each occurrence, is selected from 0, 1, and 2; and,

t, at each occurrence, is selected from 0, 1, 2, and 3.

[2] Thus, in another embodiment, the present invention provides a novel compound selected from the group:

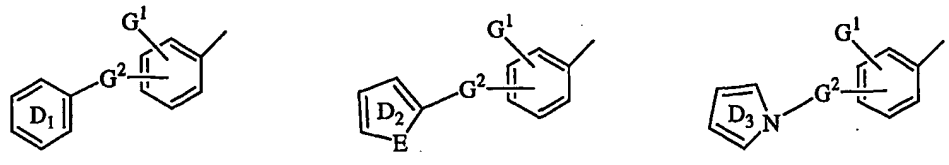






or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

G is selected from formulas Ia_1-Ic_1:



Ia_1 Ib_1 Ic_1

ring D_2 is a 5-membered heteroaromatic ring system comprising E, carbon atoms, and 0-2 N atoms, wherein E is selected from O, S, and N-D_{1c} and ring D_2 is substituted with 1 D_{1a} and 0-1 D_{1b};

ring D_3 is a 5-membered heteroaromatic ring system comprising carbon atoms and from 0-3 additional N atoms and ring D_3 is substituted with 1 D_{1a} and 0-1 D_{1b};

G^1 is selected from H, Cl, F, Br, I, OH, C_{1-3} alkoxy, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl)$_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), and $CH_2CH_2N(C_{1-3}$ alkyl)$_2$;

D_{1a} is selected from H, OH, SH, C_{1-3} alkoxy, C_{1-3} thioalkoxy, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl)$_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), and $CH_2CH_2N(C_{1-3}$ alkyl)$_2$;

D_{1b} is selected from H, C_{1-4} alkyl, Cl, F, Br, I, OH, C_{1-3} alkoxy, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl)$_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), and $CH_2CH_2N(C_{1-3}$ alkyl)$_2$;

D_{1c} is selected from H, C_{1-4} alkyl, C_{1-3} alkoxy, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl)$_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), and $CH_2CH_2N(C_{1-3}$ alkyl)$_2$;

Z is selected from a bond, CH_2O, OCH_2, CH_2NH, $NHCH_2$, $NHC(=CH_2)$, $C(O)$, $CH_2C(O)$, $C(O)CH_2$, $NHC(O)$, $C(O)NH$, $NHC(O)NH$, $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$, provided that Z does not form a N-N, N-O, NCH_2N, or NCH_2O bond with ring M or group A;

A is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^4;

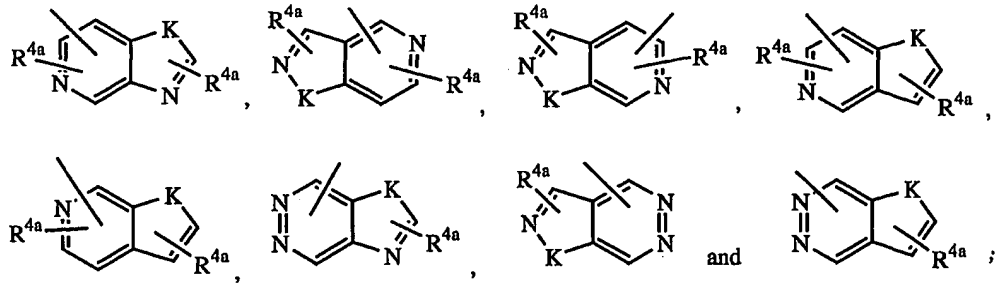
phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

X is selected from C_{1-4} alkylene, $-C(O)-$, $-C(=NR)-$, $-CR^2(NR^2R^{2a})-$, $-C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-C(O)NR^2CR^2R^{2a}-$, $-NR^2C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)NR^2-$, $-CR^2R^{2a}NR^2C(O)-$, $-NR^2C(O)NR^2-$, $-NR^2-$, $-NR^2CR^2R^{2a}-$, $-CR^2R^{2a}NR^2-$, O, $-CR^2R^{2a}O-$, and $-OCR^2R^{2a}-$;

alternatively, Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a};

cyclopropyl, cyclopentyl, cyclohexyl, phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

alternatively, Y is selected from the following bicyclic heteroaryl ring systems:



K is selected from O, S, NH, and N;

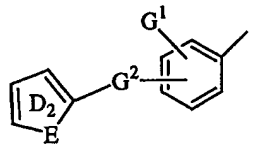
R^4, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $C(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, CF_3, NCH_2R^{1c}, OCH_2R^{1c}, SCH_2R^{1c}, $N(CH_2)_2(CH_2)_tR^{1b}$,

$O(CH_2)_2(CH_2)_tR^{1b}$, $S(CH_2)_2(CH_2)_tR^{1b}$, 5-6 membered carbocycle substituted with 0-1 R^5, and 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-1 R^5; and,

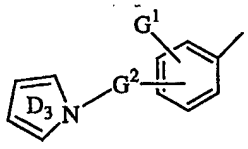
R^{4a}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, CF_3, F, Br, Cl, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $NR^2SO_2R^5$, $C(O)NHSO_2$-C_{1-4} alkyl, $S(O)_pR^5$, 5-6 membered carbocycle substituted with 0-1 R^5, and 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-1 R^5.

[3] Thus, in another embodiment, the present invention provides a novel compound, wherein:

G is selected from formulas Ib_1 and Ic_1:



Ib_1



Ic_1

ring D_2 is a 5-membered heteroaromatic ring system comprising E, carbon atoms, and 0-2 N atoms, wherein E is selected from O, S, and N-D_{1c} and ring D_2 is substituted with 1 D_{1a} and 0-1 D_{1b};

G^1 is selected from H, Cl, F, Br, I, OH, C_{1-3} alkoxy, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), and $CH_2N(C_{1-3}$ alkyl)$_2$;

D_{1a} is selected from H, OH, SH, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), and $CH_2N(C_{1-3}$ alkyl)$_2$;

D_{1b} is selected from H, C_{1-4} alkyl, Cl, F, Br, I, OH, C_{1-3} alkoxy, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), and $CH_2N(C_{1-3}$ alkyl)$_2$;

D_{1c} is selected from H, C_{1-4} alkyl, C_{1-3} alkoxy, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), and $CH_2N(C_{1-3}$ alkyl)$_2$;

Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a};

phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazole, thiadiazole, triazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-triazole, 1,3,4-triazole, benzofuran, benzothiofuran, indole, benzimidazole, benzimidazolone, benzoxazole, benzthiazole, indazole, benzisoxazole, benzisothiazole, and isoindazole;

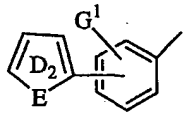
Z is selected from a bond, CH_2O, OCH_2, NH, CH_2NH, $NHCH_2$, $CH_2C(O)$, $C(O)CH_2$, $C(O)NH$, $NHC(O)$, $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$, provided that Z does not form a N-N, N-O, N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

R^4, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $C(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, CF_3, 5-6 membered carbocycle substituted with 0-1 R^5, and 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-1 R^5; and,

R^{4a}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, CF_3, F, Br, Cl, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $C(O)NHSO_2$-C_{1-4} alkyl, $S(O)_pR^5$, 5-6 membered carbocycle substituted with 0-1 R^5, and 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-1 R^5.

[4] In a preferred embodiment, the present invention provides a novel compound, wherein:

G is of formula Ib_2:



Ib_2

ring D_2 is a 5-membered heteroaromatic ring system comprising E, carbon atoms, and 0-2 N atoms, wherein E is selected from O, S, and N-D_{1c} and ring D_2 is substituted with 1 D_{1a} and 0-1 D_{1b};

G^1 is selected from H, Cl, F, Br, I, OH, C_{1-3} alkoxy, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), and $CH_2N(C_{1-3}$ alkyl$)_2$;

D_{1a} is selected from H, OH, SH, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), and $CH_2N(C_{1-3}$ alkyl$)_2$;

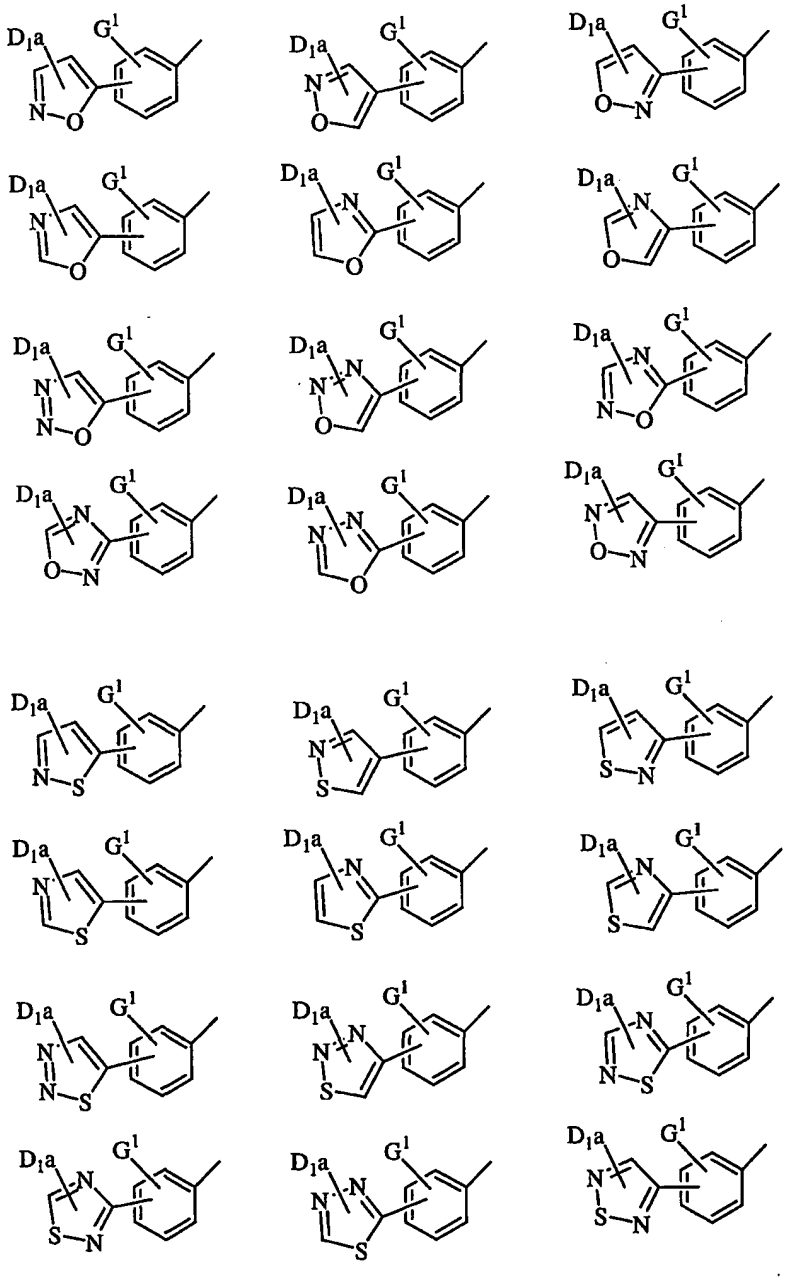
D_{1b} is selected from H, C_{1-4} alkyl, Cl, F, Br, I, OH, C_{1-3} alkoxy, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), and $CH_2N(C_{1-3}$ alkyl$)_2$;

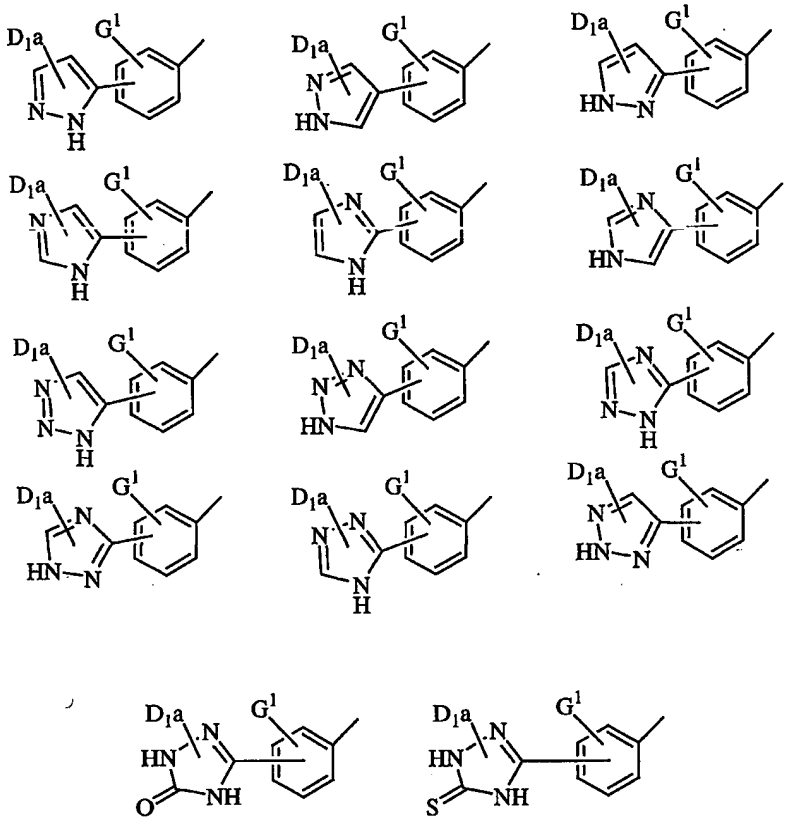
D_{1c} is selected from H, C_{1-4} alkyl, C_{1-3} alkoxy, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), and $CH_2N(C_{1-3}$ alkyl$)_2$; and,

R is selected from H, Cl, F, Br, I, $(CH_2)_tOR^3$, C_{1-4} alkyl, OCF_3, CF_3, $C(O)NR^7R^8$, $(CR^8R^9)_tNR^7R^8$ and $(CH_2)_tNR^2SO_2$-CH_3.

[5] In a more preferred embodiment, the present invention provides a novel compound, wherein:

G is selected from the group:





Z is selected from $C(O)CH_2$ and C(O)NH, provided that Z does not form a N-N bond with group A;

A is selected from phenyl, piperidinyl, pyridyl, and pyrimidyl, and is substituted with 0-2 R^4; and,

B is selected from phenyl, pyrrolidino, N-pyrrolidino-carbonyl, morpholino, N-morpholino-carbonyl, 1,2,3-triazolyl, imidazolyl, and benzimidazolyl, and is substituted with 0-1 R^{4a};

R^2, at each occurrence, is selected from H, CH_3, CH_2CH_3, cyclopropylmethyl, cyclobutyl, and cyclopentyl;

R^{2a}, at each occurrence, is selected from H, CH_3, and CH_2CH_3;

alternatively, R^2 and R^{2a}, together with the atom to which they are attached, combine to form pyrrolidine substituted with 0-2 R^{4b} or piperidine substituted with 0-2 R^{4b};

R^4, at each occurrence, is selected from OH, OR^2, $(CH_2)OR^2$, $(CH_2)_2OR^2$, F, Br, Cl, I, C_{1-4} alkyl, NR^2R^{2a}, $(CH_2)NR^2R^{2a}$, $(CH_2)_2NR^2R^{2a}$, CF_3, and $(CF_2)CF_3$;

R^{4a} is selected from C_{1-4} alkyl, CF_3, OR^2, $(CH_2)OR^2$, $(CH_2)_2OR^2$, NR^2R^{2a}, $(CH_2)NR^2R^{2a}$, $(CH_2)_2NR^2R^{2a}$, SR^5, $S(O)R^5$, $S(O)_2R^5$, $SO_2NR^2R^{2a}$, and 1-CF_3-tetrazol-2-yl;

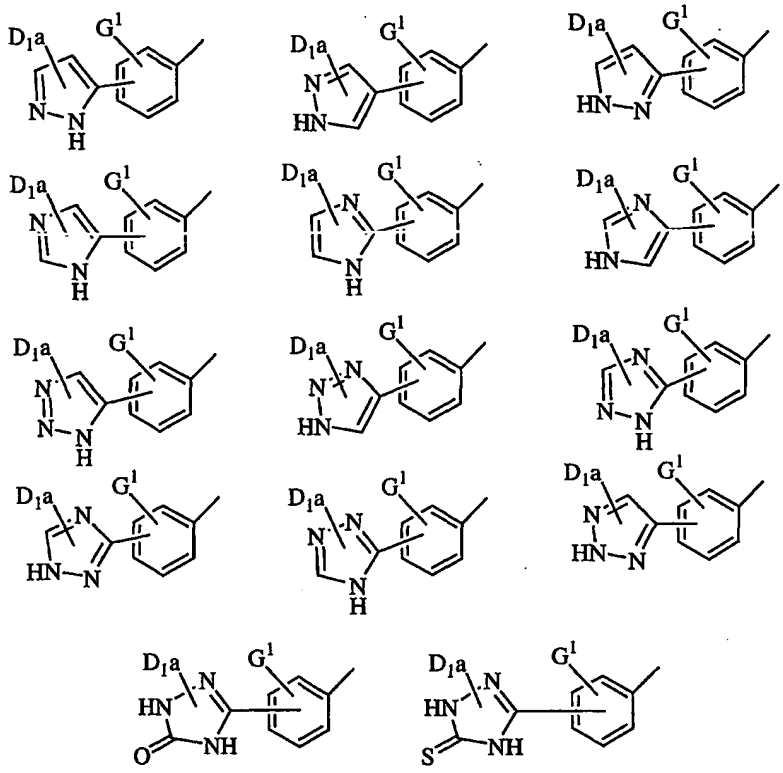
R^{4b}, at each occurrence, is selected from H, CH_3, and OH;

R^5, at each occurrence, is selected from CF_3, C_{1-6} alkyl, phenyl, and benzyl; and,

r, at each occurrence, is selected from 0, 1, and 2.

[6] In an even further preferred embodiment, the present invention provides a novel compound, wherein:

G is selected from:

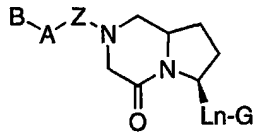


A is selected from the group: phenyl, piperidinyl, 2-pyridyl, 3-pyridyl, 2-pyrimidyl, 2-Cl-phenyl, 3-Cl-phenyl, 2-F-phenyl, 3-F-phenyl, 2-methylphenyl, 2-aminophenyl, and 2-methoxyphenyl; and,

B is selected from the group: 2-(aminosulfonyl)phenyl, 2-(methylaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl, 2-(methylsulfonyl)phenyl, 2-(N,N-dimethylaminomethyl)phenyl, 2-(N-methylaminomethyl)phenyl, 2-(N-ethyl-N-methylaminomethyl)phenyl, 2-(N-pyrrolidinylmethyl)phenyl, 1-methyl-2-imidazolyl, 2-methyl-1-imidazolyl, 2-(dimethylaminomethyl)-1-imidazolyl, 2-(methylaminomethyl)-1-imidazolyl, 2-(N-(cyclopropylmethyl)aminomethyl)phenyl, 2-(N-(cyclobutyl)aminomethyl)phenyl, 2-(N-

(cyclopentyl)aminomethyl)phenyl, 2-(N-(4-hydroxypiperidinyl)methyl)phenyl, and 2-(N-(3-hydroxypyrrolidinyl)methyl)phenyl.

[7] In another even more preferred embodiment, the present invention provides a compound of formula:



L_n is $*CH_2NHC(O)CH_2$ or $*CH(R^a)NHC(O)CH_2$, the * indicates where L_n is bonded to G;

R^a is $C(O)C(O)OR^3$;

Z is selected from a C_{1-4} alkylene, $(CH_2)_rC(O)$, and $(CH_2)_rS(O)_2$;

R^2, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2b}, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2c}, at each occurrence, is selected from OH, OCH_3, OCH_2CH_3, CH_3, benzyl, and phenyl;

R^3, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

A is C_{5-6} carbocyclic residue substituted with 0-2 R^4;

R^4, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_pR^5$, and CF_3;

R^5, at each occurrence, is selected from CF_3, C_{1-6} alkyl, phenyl, and benzyl;

p, at each occurrence, is selected from 0, 1, and 2; and,

r, at each occurrence, is selected from 0, 1, 2, and 3.

[8] In another still more preferred embodiment, the present invention provides a compound wherein:

L_n is $*CH(R^a)NHC(O)CH_2$;

R^a is $C(O)C(O)OH$;

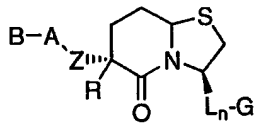
Z is selected from a CH_2, $(CH_2)_2C(O)$, and $CH_2S(O)_2$;

A is cyclohexyl or phenyl and is substituted with 0-1 R^4;

R^4, at each occurrence, is selected from H, =O, OR^2, CH_2OR^2, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3; and,

r, at each occurrence, is selected from 0, 1, and 2.

[9] In another even more preferred embodiment, the present invention provides a compound of formula:



L_n is $*CH_2NHC(O)CH_2$ or $*CH(R^a)NHC(O)CH_2$, the * indicates where L_n is bonded to G;

R^a is $C(O)C(O)OR^3$;

R is H or NH_2;

Z is selected from a C_{1-4} alkylene, $(CH_2)_rC(O)$, and $(CH_2)_rS(O)_2$;

R^2, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2b}, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2c}, at each occurrence, is selected from OH, OCH_3, OCH_2CH_3, CH_3, benzyl, and phenyl;

R^3, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

A is a C_{5-6} carbocyclic residue substituted with 0-2 R^4;

R^4, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_pR^5$, and CF_3;

R^5, at each occurrence, is selected from CF_3, C_{1-6} alkyl, phenyl, and benzyl;

p, at each occurrence, is selected from 0, 1, and 2; and,

r, at each occurrence, is selected from 0, 1, 2, and 3.

[10] In another still more preferred embodiment, the present invention provides a compound wherein:

L_n is $*CH(R^a)NHC(O)CH_2$;

R is H;

R^a is C(O)C(O)OH;

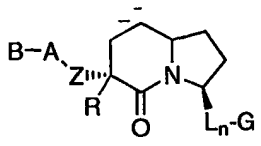
Z is selected from a CH_2, $(CH_2)_2C(O)$, and $CH_2S(O)_2$;

A is cyclohexyl or phenyl and is substituted with 0-1 R^4;

R^4, at each occurrence, is selected from H, =O, OR^2, CH_2OR^2, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3;

r, at each occurrence, is selected from 0, 1, 2, and 3.

[11] In another even more preferred embodiment, the present invention provides a compound of formula:



L_n is $*CH_2NHC(O)CH_2$ or $*CH(R^a)NHC(O)CH_2$, the * indicates where L_n is bonded to G;

R is H or NH_2;

R^a is $C(O)C(O)OR^3$;

Z is C_{1-4} alkylene;

R^2, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2b}, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2c}, at each occurrence, is selected from OH, OCH_3, OCH_2CH_3, CH_3, benzyl, and phenyl;

R^3, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

A is phenyl substituted with 0-2 R^4;

R^4, at each occurrence, is selected from H, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_pR^5$, and CF_3;

R^5, at each occurrence, is selected from CF_3, C_{1-6} alkyl, phenyl, and benzyl;

p, at each occurrence, is selected from 0, 1, and 2; and,

r, at each occurrence, is selected from 0, 1, 2, and 3.

[12] In another still more preferred embodiment, the present invention provides a compound wherein:

L_n is $*CH(R^a)NHC(O)CH_2$;

R is NH_2;

R^a is C(O)C(O)OH;

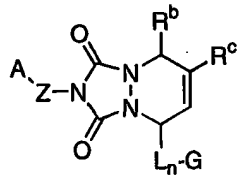
Z is CH_2;

A is phenyl substituted with 0-1 R^4;

R^4, at each occurrence, is selected from H, OR^2, CH_2OR^2, F, Cl, Br, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3; and,

r, at each occurrence, is selected from 0, 1, and 2.

[13] In another even more preferred embodiment, the present invention provides a compound of formula:



L_n is $*CH_2NHC(O)$ or $*CH(R^a)NHC(O)$ and the * indicates where L_n is bonded to G;

R^a is selected from $C(O)C(O)OR^3$ and C(O)-A;

R^b is selected from H, phenyl, C_{1-10} alkyl, and C_{2-5} alkenyl;

R^c is selected from H and C_{1-6} alkyl;

alternatively, R^b and R^c together are $-(CH_2)_4-$;

Z is $(CR^8R^9)_{1-4}$;

R^2, at each occurrence, is selected from H, CF_3, and C_{1-6} alkyl;

R^{2a}, at each occurrence, is selected from H, CF_3, and C_{1-6} alkyl;

R^{2b}, at each occurrence, is selected from H, CF_3, and C_{1-6} alkyl;

R^{2c}, at each occurrence, is selected from OH, OCH_3, OCH_2CH_3, CH_3, benzyl, and phenyl;

R^3, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

A is selected from:

C_{6-10} aromatic carbocyclic residue substituted with 0-2 R^4, and

5-10 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4;

R^4, at each occurrence, is selected from H, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_pR^5$, and CF_3;

R^5, at each occurrence, is selected from CF_3, C_{1-6} alkyl, phenyl, and benzyl;

R^8, at each occurrence, is selected from H, C_{1-6} alkyl and phenyl;

R^9, at each occurrence, is selected from H, C_{1-6} alkyl and phenyl;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, and 3.

[14] In another still more preferred embodiment, the present invention provides a compound wherein:

L_n is *CH(R^a)NHC(O) and the * indicates where L_n is bonded to G;

R^a is C(O)C(O)OH or C(O)-(benzothiazol-2-yl);

R^b is selected from H, phenyl, C_{1-10} alkyl, and C_{2-5} alkenyl;

R^c is selected from H and C_{1-6} alkyl;

alternatively, R^b and R^c together are $-(CH_2)_4-$;

Z is $(CR^8H)_{1-2}$;

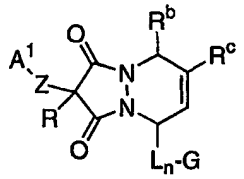
A is selected from phenyl, naphthyl, and thienyl, and A is substituted with 0-1 R^4;

R^4, at each occurrence, is selected from H, OR^2, CH_2OR^2, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3;

R^8, at each occurrence, is selected from H, methyl and phenyl; and,

r, at each occurrence, is selected from 0, 1, and 2.

[15] In another even more preferred embodiment, the present invention provides a compound of formula:



L_n is $*CH_2NHC(O)$ or $*CH(R^a)NHC(O)$ and the * indicates where L_n is bonded to G;

R^a is selected from $C(O)C(O)OR^3$ and C(O)-A;

R^b is selected from H, phenyl, C_{1-10} alkyl, and C_{2-5} alkenyl;

R^c is selected from H and C_{1-6} alkyl;

alternatively, R^b and R^c together are $-(CH_2)_4-$;

R is selected from H, benzyl, C_{1-4} alkyl, and NH_2;

Z is $(CR^8R^9)_{1-4}$;

R^2, at each occurrence, is selected from H, CF_3, and C_{1-6} alkyl;

R^{2a}, at each occurrence, is selected from H, CF_3, and C_{1-6} alkyl;

R^{2b}, at each occurrence, is selected from H, CF_3, and C_{1-6} alkyl;

R^{2c}, at each occurrence, is selected from OH, OCH_3, OCH_2CH_3, CH_3, benzyl, and phenyl;

R^3, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

A is selected from:

C_{6-10} aromatic ring substituted with 0-2 R^4, and

5-10 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4;

R^4, at each occurrence, is selected from H, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_pR^5$, and CF_3;

R^5, at each occurrence, is selected from CF_3, C_{1-6} alkyl, phenyl, and benzyl;

R^8, at each occurrence, is selected from H, C_{1-6} alkyl and phenyl;

R^9, at each occurrence, is selected from H, C_{1-6} alkyl and phenyl;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, and 3.

[16] In another still more preferred embodiment, the present invention provides a compound wherein:

L_n is *CH(R^a)NHC(O) and the * indicates where L_n is bonded to G;

R^a is C(O)C(O)OH or C(O)-(benzothiazol-2-yl);

R^b is selected from H, phenyl, C_{1-10} alkyl, and C_{2-5} alkenyl;

R^c is selected from H and C_{1-6} alkyl;

alternatively, R^b and R^c together are $-(CH_2)_4-$;

Z is $(CR^8H)_{1-2}$;

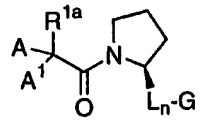
A is selected from phenyl, naphthyl, and thienyl, and A is substituted with 0-1 R^4;

R^4, at each occurrence, is selected from H, OR^2, CH_2OR^2, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3;

R^8, at each occurrence, is selected from H, C_{1-6} alkyl and phenyl;

r, at each occurrence, is selected from 0, 1, and 2.

[17] In another even more preferred embodiment, the present invention provides a compound of formula:



L_n is $*CH_2NHC(O)$ or $*CH(R^a)NHC(O)$ and the * indicates where L_n is bonded to G;

R^{1a} is selected from $-(CH_2)_r-R^{1b}$ and $NHCH_2R^{1c}$;

R^{1b} is selected from H, OR^2, NR^2R^{2a}, and $NR^2SO_2(CH_2)_rR^{2b}$;

R^{1c} is selected from $C(O)NR^2R^{2a}$, $S(O)_2R^{2b}$, and $SO_2NR^2R^{2a}$;

R^2, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2b}, at each occurrence, is selected from C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, phenyl substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-2 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2c}, at each occurrence, is selected from OH, OCH_3, OCH_2CH_3, CH_3, benzyl, and phenyl;

alternatively, R^2 and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

R^3, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

A is phenyl substituted with 0-2 R^4;

A^1 is H or A;

alternatively, A and A^1 and the carbon to which they are attached combine to form fluorene;

A^2 is selected from H, A, and CHA^3A^4;

A^3 is selected from H, A, C_{1-4} alkyl, and $-(CH_2)_rNR^2R^{2a}$;

A^4 is H or A;

R^4, at each occurrence, is selected from H, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_pR^5$, and CF_3;

R^{4b}, at each occurrence, is selected from H, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_pR^5$, and CF_3;

R^5, at each occurrence, is selected from CF_3, C_{1-6} alkyl, phenyl, and benzyl;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, and 3.

[18] In another still more preferred embodiment, the present invention provides a compound wherein:

L_n is $*CH_2NHC(O)$ and the * indicates where L_n is bonded to G;

R^{1a} is selected from $-(CH_2)_r-R^{1b}$ and $NHCH_2R^{1c}$;

R^{1b} is selected from OH, NR^2R^{2a}, and $NR^2SO_2(CH_2)_rR^{2b}$;

R^{1c} is selected from $C(O)NR^2R^{2a}$, $S(O)_2R^{2b}$, and $SO_2NR^2R^{2a}$;

R^2, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2b}, at each occurrence, is selected from C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, phenyl substituted with 0-1 R^{4b}, and pyrrolidinyl substituted with 0-1 R^{4b};

R^{2c}, at each occurrence, is selected from OH, OCH_3, OCH_2CH_3, CH_3, benzyl, and phenyl;

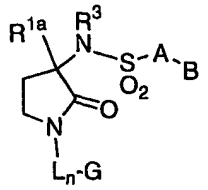
alternatively, R^2 and R^{2a}, together with the atom to which they are attached, combine to form a piperidine ring substituted with 0-1 R^{4b};

R^4, at each occurrence, is selected from H, =O, OR^2, CH_2OR^2, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3;

R^{4b}, at each occurrence, is selected from H, =O, OH, F, Cl, C_{1-4} alkyl, and NH_2; and,

r, at each occurrence, is selected from 0, 1, and 2.

[19] In another even more preferred embodiment, the present invention provides a compound of formula:



L_n is CH_2;

R^{1a} is $-(CH_2)_r-R^{1b}$;

R^{1b} is selected from H, C_{1-3} alkyl, $(CH_2)_rOR^2$, NR^2R^{2a}, $C(O)R^{2c}$, phenyl substituted with 0-2 R^4, and 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4;

R^2, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2b}, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2c}, at each occurrence, is selected from OH, OCH_3, OCH_2CH_3, CH_3, benzyl, and phenyl;

R^3, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

A is selected from:

C_{6-10} aromatic ring substituted with 0-2 R^4, and

5-10 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4;

B is selected from: H, Y, and X-Y

X is selected from C_{1-4} alkylene, $-NR^2-$, and O;

Y is selected from:

C_{6-10} aromatic ring substituted with 0-2 R^{4a}, and

5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

R^4, at each occurrence, is selected from H, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_pR^5$, and CF_3;

R^{4a}, at each occurrence, is selected from H, $(CH_2)_rOR^2$, Cl, Br, F, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_pR^5$, and CF_3;

R^5, at each occurrence, is selected from CF_3, C_{1-6} alkyl, phenyl, and benzyl;

p, at each occurrence, is selected from 0, 1, and 2; and,

r, at each occurrence, is selected from 0, 1, 2, and 3.

[20] In another still more preferred embodiment, the present invention provides a compound wherein:

R^{1a} is $-(CH_2)_r-R^{1b}$;

R^{1b} is selected from H, C_{1-3} alkyl, OH, NR^2R^{2a}, and phenyl substituted with 0-2 R^4;

A is selected from:

phenyl substituted with 0-2 R^4, naphthyl substituted with 0-2 R^4, thienyl substituted with 0-2 R^4, benzothienyl substituted with 0-2 R^4, 5-aza-benzothienyl substituted with 0-2 R^4, 6-azabenzothienyl substituted with 0-2 R^4, and quinolinyl substituted with 0-2 R^4;

B is selected from: H, Y, and X-Y

X is O;

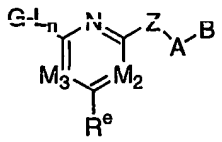
Y is phenyl substituted with 0-1 R^{4a};

R^4, at each occurrence, is selected from H, OR^2, CH_2OR^2, F, Cl, Br, I, C_{1-4} alkyl, -CN, $(CH_2)_rNR^2R^{2a}$, $C(O)NR^2R^{2a}$, and CF_3;

R^{4a}, at each occurrence, is selected from H, OR^2, CH_2OR^2, F, Cl, Br, I, C_{1-4} alkyl, -CN, $(CH_2)_rNR^2R^{2a}$, $C(O)NR^2R^{2a}$, and CF_3; and,

r, at each occurrence, is selected from 0, 1, and 2.

[21] In another even more preferred embodiment, the present invention provides a compound of formula:



L_n is O or S;

M^2 is N or CR^f;

M^3 is N or CR^d;

provided that only one of M^2 and M^3 is N;

R^e is selected from H, $N(CH_3)(CH_2CO_2H)$ and S-(5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4);

R^d is selected from H, F, and Cl;

alternatively, R^d and R^e combine to form $-NR^3-C(O)-C(R^{1g}R^3)-NR^3-$ or $-N=CR^2-NR^3-$;

R^f is selected from H, F, and Cl;

alternatively, R^e and R^f combine to form $-NR^3-C(R^{1g}R^3)-C(O)-NR^3-$ or $-NR^3-CR^2=N-$;

Z is O, provided that Z does not form a N-O or NCH_2O bond with the groups to which Z is attached;

R^{1g} is selected from H, C_{1-6} alkyl, and C_{1-6} alkyl substituted with A;

R^2, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2b}, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2c}, at each occurrence, is selected from OH, OCH_3, OCH_2CH_3, CH_3, benzyl, and phenyl;

R^3, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

A is selected from:

C_{5-6} carbocyclic residue substituted with 0-2 R^4, and

5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4;

B is H or Y;

Y is selected from:

C_{5-6} carbocyclic residue substituted with 0-2 R^{4a}, and

5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

R^4, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3;

R^{4a}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, $(CH_2)_r$-F, $(CH_2)_r$-Br, $(CH_2)_r$-Cl, Cl, Br, F, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3; and,

r, at each occurrence, is selected from 0, 1, 2, and 3.

[22] In another still more preferred embodiment, the present invention provides a compound wherein:

L_n is O;

R^e is $N(CH_3)(CH_2CO_2H)$;

R^d is H or F;

alternatively, R^d and R^e combine to form $-NR^3-C(O)-C(R^{1g}R^3)-NR^3-$ or $-N=CR^2-NR^3-$;

R^f is H or F;

alternatively, R^e and R^f combine to form $-NR^3-C(R^{1g}R^3)-C(O)-NR^3-$ or $-NR^3-CR^2=N-$;

R^{1g} is selected from H, C_{1-2} alkyl and benzyl;

A is phenyl substituted with 0-2 R^4;

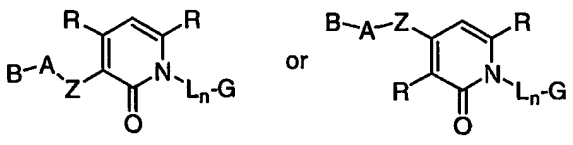
B is H or Y;

Y is 5 membered heterocyclic system containing from 1-2 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

R^4, at each occurrence, is selected from H, C_{1-4} alkyl, and NR^2R^{2a}; and,

R^{4a}, at each occurrence, is selected from H, C_{1-4} alkyl, and NR^2R^{2a}.

[23] In another even more preferred embodiment, the present invention provides a compound of formula:



L_n is $*CH_2NHC(O)CH_2$ or $*CH(R^a)NHC(O)CH_2$ and the * indicates where L_n is bonded to G;

R^a is $C(O)C(O)OR^3$;

R, at each occurrence, is selected from H, Cl, F, Br, I, OR^3, C_{1-4} alkyl, $C(O)NH_2$, and NH_2;

Z is selected from a C_{1-4} alkylene and $(CH_2)_rSO_2NR^3$;

R^2, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2c}, at each occurrence, is selected from OH, OCH_3, OCH_2CH_3, CH_3, benzyl, and phenyl;

R^3, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

A is selected from:

C_{5-6} carbocyclic residue substituted with 0-2 R^4, and

5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4;

B is selected from: H, Y, and X-Y

alternatively, when B is H, A is $(phenyl)_2CH$- substituted with 0-2 R^4;

X is selected from C_{1-4} alkylene, -C(O)-, $-NR^2-$, and O;

Y is selected from:

C_{5-6} carbocyclic residue substituted with 0-2 R^{4a}, and

5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

R^4, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3;

R^{4a}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, Cl, Br, F, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3; and,

r, at each occurrence, is selected from 0, 1, 2, and 3.

[24] In another still more preferred embodiment, the present invention provides a compound wherein:

L_n is $*CH_2NHC(O)CH_2$ and the * indicates where L_n is bonded to G;

R, at each occurrence, is selected from H and C_{1-4} alkyl;

Z is $CH_2SO_2NR^3$;

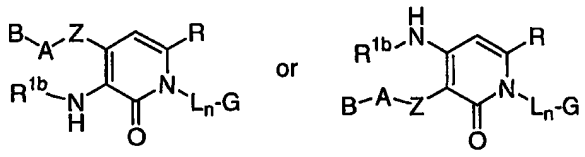
A is phenyl substituted with 0-2 R^4;

B is H;

R^4, at each occurrence, is selected from H, $(CH_2)_rOR^2$, F, Cl, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, and $C(O)NR^2R^{2a}$; and,

r, at each occurrence, is selected from 0, 1, and 2.

[25] In another even more preferred embodiment, the present invention provides a compound of formula:



L_n is $*CH_2NHC(O)CH_2$ or $*CH(R^a)NHC(O)CH_2$ and the * indicates where L_n is bonded to G;

R^a is $C(O)C(O)OR^3$;

R, at each occurrence, is selected from H, C_{1-4} alkyl, and NH_2;

R^{1g} is H or C_{1-6} alkyl;

Z is selected from a C_{1-4} alkylene and $(CH_2)_rS(O)_p(CH_2)_r$;

R^2, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2c}, at each occurrence, is selected from OH, OCH_3, OCH_2CH_3, CH_3, benzyl, and phenyl;

R^3, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

A is selected from:

C_{3-6} carbocyclic residue substituted with 0-2 R^4, and

5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4;

B is selected from: H, Y, and X-Y

alternatively, when B is H, A is $(phenyl)_2CH$- substituted with 0-2 R^4;

X is selected from C_{1-4} alkylene, -C(O)-, $-NR^2-$, and O;

Y is selected from:

C_{5-6} carbocyclic residue substituted with 0-2 R^{4a}, and

5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

alternatively, Z-A-B combine to form S-C_{1-6} alkyl;

R^4, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3;

R^{4a}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, Cl, Br, F, I, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3;

p is selected from 0, 1, and 2; and,

r, at each occurrence, is selected from 0, 1, 2, and 3.

[26] In another still more preferred embodiment, the present invention provides a compound wherein:

L_n is $*CH_2NHC(O)CH_2$ and the * indicates where L_n is bonded to G;

R is H or C_{1-4} alkyl;

R^{1g} is H;

Z is CH_2, CH_2S, or $CH_2S(O)_2$;

A is a C_{3-6} carbocyclic residue substituted with 0-2 R^4;

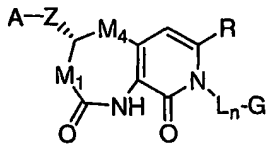
B is H

alternatively, Z-A-B combine to form S-C_{1-6} alkyl;

R^4, at each occurrence, is selected from H, $(CH_2)_rOR^2$, F, Cl, Br, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3; and,

r, at each occurrence, is selected from 0, 1, and 2.

[27] In another even more preferred embodiment, the present invention provides a compound of formula:



L_n is $*CH_2NHC(O)CH_2$ or $*CH(R^a)NHC(O)CH_2$ and the * indicates where L_n is bonded to G;

M^1 is absent or is selected from CHR, O, and NR^2;

M^4 is selected from NR^2, CR^f, and C(O);

R is selected from H, Cl, F, Br, I, OR^3, C_{1-4} alkyl, OCF_3, CF_3, and NH_2;

Z is C_{1-4} alkylene;

R^2, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2c}, at each occurrence, is selected from OH, OCH_3, OCH_2CH_3, CH_3, benzyl, and phenyl;

R^3, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

A is selected from:

C_{3-6} carbocyclic residue substituted with 0-2 R^4, and

5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4;

R^4, at each occurrence, is selected from H, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3; and,

r, at each occurrence, is selected from 0, 1, 2, and 3.

[28] In another still more preferred embodiment, the present invention provides a compound wherein:

L_n is $*CH_2NHC(O)CH_2$ and the * indicates where L_n is bonded to G;

M^1 is absent;

R is selected from H and C_{1-4} alkyl;

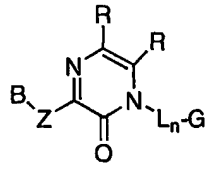
Z is CH_2;

A is C_{3-6} carbocyclic residue substituted with 0-1 R^4;

R^4, at each occurrence, is selected from H, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, and CF_3; and,

r, at each occurrence, is selected from 0, 1, and 2.

[29] In another even more preferred embodiment, the present invention provides a compound of formula:



L_n is $*CH_2NHC(O)CH_2$ or $*CH(R^a)NHC(O)CH_2$ and the * indicates where L_n is bonded to G;

R^a is $C(O)C(O)OR^3$;

R, at each occurrence, is selected from H, Cl, F, Br, I, OR^3, C_{1-4} alkyl, $C(O)NH_2$, and NH_2;

Z is $(CHR^8)NR^3$, $(CHR^8)_2NR^3$, and $(CHR^8)_2SO_2R^3$;

provided that when Z is $(CHR^8)_2NR^3$, then B is absent;

R^2, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, C_{1-6} alkyl, benzyl, and phenyl;

R^{2c}, at each occurrence, is selected from OH, OCH_3, OCH_2CH_3, CH_3, benzyl, and phenyl;

R^3, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

R^{3a}, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

B is H or Y;

Y is selected from:

C_{5-6} carbocyclic residue substituted with 0-2 R^{4a}, and

5-6 membered heterocyclic system containing from 1-2 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

R^{4a}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, Cl, Br, F, I, C_{1-4} alkyl, -CN, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and CF_3;

R^8, at each occurrence, is selected from H, C_{1-6} alkyl and phenyl; and,

r, at each occurrence, is selected from 0, 1, 2, and 3.

[30] In another still more preferred embodiment, the present invention provides a compound wherein:

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(74) Agent: **BELFIELD, Jing, S.**; Bristol-Myers Squibb Pharma Company, Route 141 & Henry Clay Road, Experimental Station, E353/133B, Wilmington, DE 19898-0353 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/002519 A3

(54) Title: THROMBIN OR FACTOR Xa INHIBITORS

(57) Abstract: This invention relates generally to heteroaryl-phenyl substituted compounds that are inhibitors of trypsin-like serine protease enzymes, especially factor Xa or thrombin, pharmaceutical compositions containing the same, and methods of using the same as anticoagulant agents for treatment and prevention of thromboembolic disorders.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/20962

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/50 A61K31/50 A61K31/50 A61K31/50
//(C07D487/04,241:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 28326 A (SIDDIQUI M ARSHAD ;BACHAND BENOIT (CA); IAF BIOCHEM INT (CA); EDMU) 2 July 1998 (1998-07-02) cited in the application claim 28, 2 last cpds; ex. page 40 ---	1-8, 54-57
Y	WO 97 48706 A (SIDDIQUI M ARSHAD ;EDMUNDS JEREMY JOHN (US); WARNER LAMBERT CO (US) 24 December 1997 (1997-12-24) abstract; claims ---	1-8, 54-57
Y	WO 96 19483 A (IAF BIOCHEM INT ;DIMAIO JOHN (CA); SIDDIQUI M ARSHAD (CA); GILLARD) 27 June 1996 (1996-06-27) cited in the application cpds VIII, ex. 495,510,515,640,760,765 --- -/--	1-8, 54-57

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 February 2002	16. 5. 02

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Frelon, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/20962

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	L.S. NARASIMHAN ET AL.: "Structural basis of the thrombin selectivity..." JOURNAL OF MEDICINAL CHEMISTRY, vol. 43, 2000, pages 361-368, XP002188952 WASHINGTON US the whole document	1-8, 54-57
Y	ST-DENIS Y ET AL: "Potent bicyclic lactam inhibitors of thrombin: Part I: P3 modifications" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 8, no. 22, 17 November 1998 (1998-11-17), pages 3193-3198, XP004143725 ISSN: 0960-894X the whole document	1-8, 54-57
Y	PLUMMER J S ET AL: "Potent and selective bicyclic lactam inhibitors of thrombin: part 2: P1 modifications" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 8, no. 23, 1 December 1998 (1998-12-01), pages 3409-3414, XP004143767 ISSN: 0960-894X the whole document	1-8, 54-57
Y	PLUMMER J S ET AL: "Potent and selective bicyclic lactam inhibitors of thrombin: part 3: P1' modifications" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 6, 22 March 1999 (1999-03-22), pages 835-840, XP004160484 ISSN: 0960-894X the whole document	1-8, 54-57
A	WO 98 57937 A (DU PONT MERCK PHARMA) 23 December 1998 (1998-12-23) page 191; example 73	1-8, 54-57
A	WO 97 23212 A (DU PONT MERCK PHARMA) 3 July 1997 (1997-07-03) claim 1: cpds IIIa,IIIb	1-8, 54-57

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/20962

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 53
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-6,7,8,54,56-57 all in part

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-6(in part),7,8,54(in part),56-57(in part)

   Compounds first designated in claim 1, corresponding to compounds claimed in claim 7 and dependent claims thereof

2. Claims: 1-6(in part),9,10,54(in part),56-57(in part)

   Compounds further designated in claim 1, corresponding to compounds claimed in claim 9 and dependent claims thereof

3. Claims: 1-6(in part),11,12,54(in part),56-57(in part)

   Compounds further designated in claim 1, corresponding to compounds claimed in claim 11 and dependent claims thereof

4. Claims: 1-6(in part),13,14,54(in part),56-57(in part)

   Compounds further designated in claim 1, corresponding to compounds claimed in claim 13 and dependent claims thereof

5. Claims: 1-6(in part),15,16,54(in part),56-57(in part)

   Compounds further designated in claim 1, corresponding to compounds claimed in claim 15 and dependent claims thereof

6. Claims: 1-6(in part),17,18,54(in part),56-57(in part)

   Compounds further designated in claim 1, corresponding to compounds claimed in claim 17 and dependent claims thereof

7. Claims: 1-6(in part),19,20,54(in part),56-57(in part)

   Compounds further designated in claim 1, corresponding to compounds claimed in claim 19 and dependent claims thereof

8. Claims: 1-6(in part),21,22,54(in part),56-57(in part)

   Compounds further designated in claim 1, corresponding to compounds claimed in claim 21 and dependent claims thereof

9. Claims: 1-6(in part),23,24,54(in part),56-57(in part)

   Compounds further designated in claim 1, corresponding to compounds claimed in claim 23 and dependent claims thereof

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

10. Claims: 1-6(in part),25,26,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 25 and dependent claims thereof

11. Claims: 1-6(in part),27,28,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 27 and dependent claims thereof

12. Claims: 1-6(in part),29,30,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 29 and dependent claims thereof

13. Claims: 1-6(in part),31,32,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 31 and dependent claims thereof

14. Claims: 1-6(in part),33,34,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 34 and dependent claims thereof

15. Claims: 1-6(in part),35,36,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 35 and dependent claims thereof

16. Claims: 1-6(in part),37,38,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 37 and dependent claims thereof

17. Claims: 1-6(in part),39,40,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 39 and dependent claims thereof

18. Claims: 1-6(in part),41,42,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 41 and dependent claims thereof

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

19. Claims: 1-6(in part),43,44,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 43 and dependent claims thereof

20. Claims: 1-6(in part),45,46,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 45 and dependent claims thereof

21. Claims: 1-6(in part),47,48,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 47 and dependent claims thereof

22. Claims: 1-6(in part),49,50,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 49 and dependent claims thereof

23. Claims: 1-6(in part),51,52,54(in part),56-57(in part)

Compounds further designated in claim 1, corresponding to compounds claimed in claim 51 and dependent claims thereof

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 55 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 53

The compounds of claim 53 lack to be properly defined: firstly because they are defined by a result to be achieved (i.e. as trypsin-like serine protease enzyme inhibitors), secondly because the term "P1" is not specified in the claim and has no support in the description (i.e. the expression "inhibitor comprising a P1 group" is not searchable as such).

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nformation on patent family members

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PCT/US 01/20962

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